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Elevated *Staphylococcus* Ceftriaxone MICs are an Etest Artifact

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To the Editor

The recent publication by Pickering et al [1] described a collection of methicillin-susceptible *Staphylococcus aureus* (MSSA) that displayed elevated ceftriaxone minimum inhibitory concentrations (MICs) when tested by Etest (bioMérieux, Durham, North Carolina) gradient diffusion and would have been called “Resistant” to ceftriaxone based on previous Clinical and Laboratory Standards Institute (CLSI) interpretive guidance. The authors reported that approximately 60% of MSSA tested at their institution would have been misclassified based on the current CLSI guidance, which recommends testing staphylococci only against penicillin and oxacillin or cefoxitin in order to infer susceptibility or resistance to other β -lactam agents. This article was available electronically ahead of print for several months. Although it was subsequently retracted as “an honest error in interpretation,” we believe a fuller explanation of the findings could improve understanding among *Clinical Infectious Diseases* readership.

We investigated the accuracy of the initial report by performing reference broth microdilution (BMD), disk diffusion, and Etest [both low (0.002–32 μ g/mL) and high (0.016–256 μ g/mL) range ceftriaxone Etest products] antimicrobial susceptibility testing on 8 pulsed field gel electrophoresis (PFGE)-matched pairs of MSSA from the Pickering study [1] reported to have mismatched ceftriaxone susceptibility. All 16 isolates were confirmed as oxacillin, cefoxitin, and ceftriaxone susceptible [2, 3] with BMD and disk methods. Ceftriaxone MICs obtained by both Etest products were typically higher than those obtained with BMD but were still in the susceptible range for 100% of isolates using the high concentration ceftriaxone Etest, and for 93.8% of isolates using the low concentration ceftriaxone Etest (1 isolate tested as intermediate). In addition, 30 consecutive, unique MSSA isolated from blood cultures during 2 months at a single hospital were tested against ceftriaxone by BMD, disk diffusion, and Etest using a single 0.5 McFarland inoculum. All isolates tested ceftriaxone susceptible by disk diffusion and BMD; 13 (43%) isolates tested

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nonsusceptible with Etest (Table 1). We also note that the Etest ceftriaxone package inserts do not list staphylococci as an organism group for which testing has been cleared [4, 5].

In summary, it appears that the ceftriaxone resistance reported in error by Pickering et al is an artifact of inappropriate testing rather than an error in interpretation, which was apparent when reference methods were used to confirm the original findings. This report created considerable angst among the infectious disease community and will require ongoing education to dispel its conclusions. This should serve as a reminder that reports of novel antimicrobial resistance should be confirmed by a reference method prior to publication, and that antimicrobial susceptibility testing should only be performed with validated methods.

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Table 1Ceftriaxone MIC of 30 Methicillin-susceptible *S. aureus* Tested by Broth Microdilution (BMD) or Etest

	Ceftriaxone MIC Obtained	
	BMD	Etest
N (%) susceptible	30 (100)	17 (53)
Mode MIC (µg/mL)	4	8
Median MIC (µg/mL)	4	8
MIC ₅₀ (µg/mL)	4	8
MIC ₉₀ (µg/mL)	4	16

Abbreviations: BMD, broth microdilution; MIC, minimum inhibitory concentration; *S. aureus*, *Staphylococcus aureus*.